REMARKS

Claims 1-65 are pending in the application. Claims 12, 15-33, 43, 64, and 65 were withdrawn by the Examiner pursuant to a species election requirement. Thus, claims 1-11, 13, 14, 34-42, and 44-63 are currently under examination.

With entry of the instant amendment, claims 1, 6, 7, 34, 38, 40, 51, and 57 have been amended. The amendments to the claim add no new matter and are supported throughout the application as filed. For example, claims 1, 34, and 51 have been amended to reflect that the same nucleic acid binding protein specifically binds to either the first or to the second site. This amendment adds no new matter. Support can be found, *e.g.,* in the specification at page 19, lines 24-25. Claim 40 has been amended to recite that the first binding site is within 11 nucleotides of said second binding site. Support for the amendment can be found, *e.g.,* on page 3, line 31 through page 4, line 1.

For convenience, the rejections/objections are set forth in the order presented in the Office Action.

The invention

The invention provides molecular constructs that act as logic or memory elements that can operate analogously to their electronic counterparts. In the claims currently under examination, the central operational element of these devices is a nucleic acid having at least two protein binding sites, which are mutually exclusive, *i.e.,* only one site can be bound at a time. The protein that specifically binds the first and second site can be the same protein. For example, two Fis binding sites may be present in the nucleic acid. A Fis protein that binds to the first site prevents binding of a Fis protein to the second site. Similarly, binding of the Fis protein to the second site prevents binding of a Fis protein to the first site. Additional embodiments of the invention include those in which the nucleic acid has at least three protein binding sites.. These logic or memory elements can be used, for example, to regulate gene expression in cells or to provide components of a molecular binary computational or control system.

Rejections under 35 U.S.C. § 102

Claims 1-3, 6, 8, 9, 11, 34-36, 38-40, 42, 51-54, 57-59, and 61 were rejected as allegedly anticipated by Gille *et al.* (*Nucl. Acid Res.* 19:4167-4172, 1991). Gille *et al.* do not teach a nucleic acid that comprises mutually exclusive binding sites that specifically bind the same nucleic acid binding protein. Therefore, the reference does not anticipate the claimed invention. Applicants therefore respectfully request withdrawal of the rejection.

Rejections under 35 U.S.C. § 103

The claims are patentable over the combination of Gille et al. in view of Schneider

Claims 1-11, 13, 14, 34-42, and 44-63 were rejected as allegedly unpatentable over Gille *et al.*, *supra*, in view of Schneider (*J. Theor. Biol.* 148:125-137, 1991) and Schneider (*Nanotechnology* 4:1-18, 1994). The rejection alleges that it is well known in the art that different molecular systems can be used for logic operations and computation by molecular machines (*see,* the last sentence on page 4 bridging to the first sentence on page 5 of the Office Acition). The Examiner argues that genetic control systems often work by one molecule binding to a spot to prevent another molecule from binding at that site. As an example, he cites Schneider (1991) as teaching that the *lac* repressor protein only binds to the operator when it is unbound by an inducer. The Examiner contends that one of skill would have been motivated by one or both of the Schneider references to modify Gille *et al.* to test different genetic systems as molecular machines, including testing constructs that bind to EF-Tu and testing a nucleic acid that comprises two Fis binding sites that are separated by a linker of various sizes so as to permit binding of one Fis and prevent the binding of another Fis. To the extent that the rejection applies to the amended claims, Applicants respectfully traverse.

As the Examiner knows, in order to establish a *prima facie* case of obviousness, the rejection must demonstrate that: (1) there is some suggestion or motivation to modify the reference or combine the reference teachings; (2) there is a reasonable expectation of success: and (3) the prior art references suggest all the claim elements. *See, e.g.*, MPEP § 2143; *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991). At a minimum, the Examiner's arguments fail to meet at least two of these criteria: the cited references do not suggest all of the claim elements and

moreover, the arguments fail to establish why one of skill would be motivated to modify the teachings of Gille *et al.* to produce a nucleic acid that incorporates at least two mutually exclusive binding sites that specifically bind the same protein.

The two Schneider references cited by the Examiner teach that many molecules perform specific tasks which require simple decisions, such as whether or not to bind a nucleic acid sequence at a particular site. Examples of such molecular machines include the restriction enzyme *Eco*RI, which binds only at a specific recognition sequence, and the *lac* repressor, which binds to a specific binding site only when it, *i.e,* the *lac* repressor, is not bound by an inducer. The references teach that these sorts of functions can serve as the basis for logical operations and that molecular computers are possible. However, the references do not teach or suggest the particular logic or memory systems that are the subject of the instant application, and further, contrary to the Examiner's assertions, they do not teach how to build a molecular computer. Indeed, the Examiner's arguments rely on the knowledge of Applicants' disclosure in reaching a determination of *prima facie* obviousness. This is improper (*see, e.g.*, MPEP § 2142).

The Schneider references do not teach or suggest a molecular logic or memory system comprising the elements of the invention

First, the cited references do not suggest all of the elements of the claimed invention. The claims are drawn to a nucleic acid comprising two mutually exclusive binding sites that bind the same protein. Gille *et al.* describe an *oriC* fragment that comprises a Fis binding site and a DnaA binding site that appear to be mutually exclusive. These are two different binding sites. The Schneider references provide examples of proteins that bind to a specific site. None of the references contain a teaching or suggestion of at least two protein binding sites that are mutually exclusive and bind the same protein. Thus, the cited art does not teach or suggest all of the elements of the claimed invention.

Second, there is no disclosure in the Schneider references of how to build a molecular computer. The references merely disclose that it should be possible. With regard to the *Eco*RI example, the cited art teaches that the restriction enzyme binds to a specific sequence and that recognition and binding to the restriction site is basically an AND function. Where is

the teaching of how a molecular computer can be built based on this feature? The Examiner also argues that the example of the *lac* repressor shows that one molecule, the inducer, influences the binding of another molecule, the *lac* repressor, to the operon. However, here the logic resides in the protein itself, a situation that is distinct from the present invention. There is no disclosure of any way to build a computer based on the ability of the inducer to influence the binding of the *lac* repressor to the operon. Thus, the Examiner's conclusion that the Schneider publications teach "ways of building a molecular computer including using natural genetic controls systems" is not supported by the references themselves.

There is no motivation to modify the cited references

The Examiner contends that the *lac* repressor is analogous to other proteins that bind a specific site, *e.g.*, EF-Tu, and that this provides a sufficient motivation to modify the *oriC* sequences taught by Gille *et al.* to derive the claimed invention: nucleic acids comprising mutually exclusive binding sites that bind the same protein and thus serve as logic or memory elements. However, the Examiner does not provide any evidence from the art that points to these particular modifications.

Further, the Examiner fails to provide a principle known in the art that would lead the practitioner to apply the teachings of the allosteric modulation of *lac* repressor binding to the studies of the origin of chromosomal DNA replication described by Gille *et al.* The mere fact that references can be combined or modified is not sufficient to establish *prima facie* obviousness unless the prior art also suggests the desirability of the combination. Where does the prior art teach the desirability of modifying the *oriC* sequences in such a manner? Applicants submit that the Examiner can only be employing hindsight to argue that the invention is obvious. As stated by the Federal Circuit Court (*In re Rouffet*, 47 USPQ2d 1453 (Fed. Cir. 1998)), "the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed." The Examiner provides no evidence that the mere mention of molecular machines and a protein-DNA binding interaction is

sufficient to lead one of skill to the claimed invention. The "motivation" is based on the disclosure in the instant application. Accordingly, it is not proper.

Finally, the Examiner also asserts that modification of Gille *et al.* to contain two Fis binding sites, variably spaced to permit binding of one Fis and prevent the binding of another Fis, would have been obvious because Schneider motivates finding a system where binding of one molecule prevents the binding of another. Again, this argument fails. The Schneider references generally teach that molecular computers should be possible to build based on genetic control elements. The Examiner provides no reasoning that would lead one of skill to the particular combination of elements that are claimed here. What is the principle that would lead the skilled artisan to add to modify Gille *et al.* to include two Fis binding sites that are separated by a linker of varying lengths? The Examiner is essentially arguing that one of skill would have been motivated to make the invention because the invention exists.

In view of the above, the Examiner has not established a case of *prima facie* obviousness. Accordingly, the claims are patentable over the cited art. Applicants therefore respectfully request withdrawal of the rejection.

The claims are patentable over the combination of Gille et al. in view of Wickens et al.

Claims 46-50 were rejected as allegedly unpatenable over Gille *et al.* in view of Wickens *et al.* As explained above, the cited art fails to suggest each of the claimed elements and the Examiner's arguments fail to provide a proper motivation to combine the references. Wickens *et al.* do not correct these deficiencies. Thus, the claims are patentable over Gille *et a*l. in view of Wickens *et al.*. Applicants therefore respectfully request withdrawal of the rejection.

Claim objections

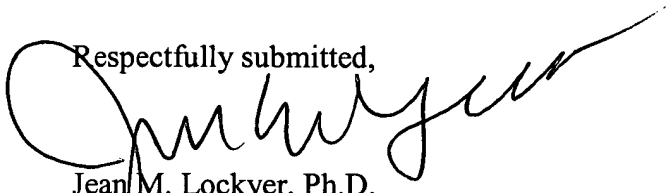
Line 12 of claim 34 was objected to because of the inadvertent period at line 12. Claim 40 is objected to as being a duplicate of claim 39. The objections are obviated in view of the amendment to claim 34 to delete the period and the amendment to claim 40 to recite that the first binding site is within 11 nucleotides of the second binding site.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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Attachments
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